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Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases

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Abstract

Patients with castration-resistant prostate cancer (CRPC) frequently have metastases to the bone, which may cause pain and lead to a deterioration in quality-of-life. Bone-seeking radiopharmaceuticals are agents which, when administered systemically, localize to the site of bone metastases and deliver focal radiation there. In this review, we will summarize the current literature on bone-targeting radiopharmaceuticals for CRPC, focusing on strontium-89, samarium-153, rhenium-186 and radium-223. We will discuss their indications, clinical efficacy, and toxicities and highlight some of the challenges in optimizing treatment with these agents. Historically, clinical trials with these drugs have failed to demonstrate survival improvements, restricting their use for palliative purposes only. Radium-223 is the first agent in this class to show an overall survival advantage in CRPC patients with bone metastases. This landmark finding will likely have a considerable impact on the treatment paradigm of bone-metastatic CRPC, and will pave the way for further developments in the future.

Keywords

Bone metastases; Castration-resistant prostate cancer; Radiopharmaceuticals; Radium-223; Samarium-153; Strontium-89

1. Introduction

An estimated 241,740 men will be diagnosed with prostate cancer in the United States this year [1], contributing to an estimated 28,170 cancer-related deaths. In patients with recurrent or advanced prostate cancer, use of androgen deprivation therapy (which acts by depleting or blocking the effects of androgens) is the standard-of-care [2–4]. Androgen deprivation usually results in initial tumor regressions with declines in prostate-specific antigen (PSA) levels and relief of symptoms in many patients, but the disease eventually progresses to a castration-resistant state [5]. Many mechanisms for castration-resistance have been postulated, including persistent androgen receptor (AR) signaling, ectopic androgen synthesis, and activation of AR-independent pathways [6]. In patients with castration-

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resistant prostate cancer (CRPC), treatment options are expanding [7] and four modalities have been FDA-approved to date based on evidence of survival prolongation in men with metastatic CRPC: docetaxel is approved as first-line chemotherapy [8], cabazitaxel is approved as second-line chemotherapy [9], the immunotherapy product sipuleucel-T is approved for asymptomatic patients [10], and the androgen biosynthesis inhibitor abiraterone is approved for docetaxel-pretreated men [11].

CRPC metastasizes frequently to the bone, an event occurring in the majority of advanced prostate cancer patients [8,12,13]. Osseous metastases are most commonly found in the axial skeleton (vertebral bodies, pelvis, ribs and skull), but may also occur in long bones (femurs, humeri). Bone scintigraphy using ^{99}technetium-methylene diphosphonate (^{99}Tc-MDP) remains the standard method for detection of osseous metastases, and is an essential component of the staging of the disease [14]. Newer modalities for the identification of bone metastases are also being investigated, and have shown encouraging results when compared with ^{99}Tc-MDP bone scans [15,16].

The extent of osseous involvement in metastatic prostate cancer has been found to be associated with patient survival [17]. Clinically, bone lesions may manifest as pain or as skeletal-related events (SREs). SREs include bone complications such as spinal-cord compression, pathological fractures, hypercalcemia of malignancy, need for bone surgery, and need for bone radiation, some of which could have devastating consequences. Additionally, patients receiving chronic androgen deprivation are especially vulnerable to fragility fractures from reduced bone-mineral density [18]. These effects can result in diminished mobility and a considerable deterioration in quality-of-life [19].

In patients with advanced CRPC, PSA elevations usually precede detectable bone lesions which in turn usually precede bone pain [20]. The development of bone metastases is thought to involve multiple cytokines and growth factors including transforming growth-factor (TGF-β), bone-morphogenic proteins (BMPs), and epidermal growth-factor (EGF) that engage in processes involving migration of prostate cells to bone tissue and cellular adhesion to bone matrix [21–24]. In patients with bone metastases, there is increased bone turnover with activation of both osteoblastic and osteoclastic activity [25,26]. Bone pain manifests in multiple forms and the exact mechanism of this pain is poorly understood. Studies have suggested the role of tumor-induced cytokines, tumor infiltration of bone matrix causing osteolysis, direct nerve injury, and stimulation of peripheral nerve endings by various substances leading to nerve sensitization causing allodynia and hyperalgesia [27]. One of the roles of radiopharmaceuticals is the reduction of these growth factors and cytokines at the interface of tumor metastases and normal bone.

Adequate treatment of metastatic bone pain is impeded by underestimation of pain by physicians, patient reluctance to report pain, and poor knowledge of treatment options [28]. Approximately 80–90% of patients with cancer pain report effective pain relief with the WHO-recommended “three-step ladder” approach [29,30]. Acetaminophen and non-steroidal anti-inflammatory drugs constitute first-line agents for pain control, although these may provide insufficient relief requiring escalation to low-potency opioids. Subsequently, stronger opioids are added in a step-wise fashion as the disease progresses. Optimal

management of bone pain requires a multi-disciplinary approach including chemotherapeutic options, osteoclast-inhibitory agents, corticosteroids, external- beam radiotherapy, or even surgery [31]. Radiopharmaceutical agents have emerged as another viable option in patients with multiple osseous metastases. These compounds are systemically-administered radioactive agents that localize to sites of bone metastases and deliver focal radiation through β-emission (strontium- 89, samarium-153, rhenium-186) or α-particles (radium-223). Bone-seeking radiopharmaceuticals have considerable advantages including easy administration, ability to treat multiple metastatic lesions simultaneously, and the possibility of combination with chemo-/radiotherapeutic agents for enhanced efficacy.

Agents comprising the current radiopharmaceutical armamentarium against prostate cancer include strontium-89, samarium- 153, rhenium-186, and the novel α-emitter radium-223. These compounds have been the subject of multiple randomized controlled trials exploring their efficacy in prostate cancer patients with bone metastases [28,32–35]. Historically, outcomes of interest in radiopharmaceutical trials included pain response, analgesic consumption, and quality-of-life. Notably, radium-223 is the first radiopharmaceutical agent to demonstrate improved survival among patients with symptomatic bone-metastatic CRPC. This is a landmark development in the current treatment paradigm of metastatic prostate cancer, and places us at the cusp of an exciting period in the development of successful treatments against CRPC.

This review will summarize the role of traditional bone-targeting radiopharmaceuticals in the management of prostate cancer with osseous metastases, and will also highlight the impact that the novel agent radium-223 could potentially have on the treatment landscape of bone-metastatic CRPC.

2. Physical properties

The nuclear properties of the radiopharmaceutical agents discussed herein are summarized in Table 1. The first use of systemic radionuclide therapy was with the advent of strontium-89 (Sr-89) in the 1940s, which was quickly followed by the discovery of phosphorus-32 (P-32) as a potential radiotherapeutic agent for cancers metastatic to bone. However, use of P-32 became increasingly unpopular due to its high bone marrow toxicity. Sr-89, a calcium analog, was approved by the Food and Drug Administration (FDA) in 1993 for treatment of painful bone metastases [36]. A pure β-emitter with only 0.01% γ-emission, Sr-89 has a maximum energy of 1.47 MeV, a mean energy of 0.58 MeV, and a half-life of 50.5 days [37]. The average soft-tissue range of this agent is 2.4 mm. Under ideal circumstances, the half-life of an agent should be long enough to enable sufficient therapeutic effect and short enough to limit myelotoxicity. The 1980s saw the development of newer agents with shorter half-lives, such as samarium-153 (Sm-153) and rhenium-186 (Re-186) [38,39]. Sm-153, which is produced by neutron bombardment of isotopically-enriched $^{153}Sm_2O_3$ in a nuclear reactor, was shown by to have an increased affinity for the bone when chelated by EDTMP (ethylenediaminetetra-methylenephosphate) [40]. Sm-153 emits β-particles with a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, an average soft-tissue range of 0.6 mm, and a half-life of 1.9 days [41]. The agent has a 28% γ-emission with a photo-peak of 0.104 MeV. Re-186 is a β- and γ-emitting radionuclide with a

half-life of 3.7 days. The maximum energy of Re-186 is 1.07 MeV, mean energy is 0.349 MeV, and average soft-tissue range is 1.1 mm [42]. Notably, the γ-emission from these agents enables localization of bone metastases through imaging, making these bone-seeking radioisotopes useful for both diagnostic and therapeutic purposes. The relatively shorter half-life of Sm-153 (compared to Sr-89 and Re-186) enables faster radiation delivery and rapid clearance from the body after intravenous injection, making it a suitable candidate for bone-targeted treatment. By contrast, Sr-89 has comparatively higher particle emissions, resulting in a greater degree of myelotoxicity.

Radium-223 (Ra-223) is an investigational α-emitting agent that is under investigation for men with symptomatic bone-metastatic CRPC. Ra-223 has a half-life of 11.4 days, and releases 94% of its energy as α-particles with very little γ-emission. It is produced from ^{227}actinium/^{227}thorium and purified using actinium-resin to immobilize ^{227}actinium and ^{227}thorium [43]. α-Emission has theoretical advantage over β-emission due to reduced marrow toxicity due to its narrow range. Similar to cationic strontium, radium-223 is a natural bone-seeker and complexes with hydroxyapatite crystals in osteoblastic bone metastases, inducing non-repairable DNA strand breaks.

3. Indications and contraindications

Bone-seeking radiopharmaceuticals are generally indicated for prostate cancer patients with painful osteoblastic metastases confirmed by bone scan [44]. External-beam radiation therapy (EBRT) to bone metastases has also been shown to provide symptomatic pain relief in up to 80% of such patients [45]. Patients with unifocal disease are better treated with EBRT while those with multifocal bone disease are excellent candidates for radiopharmaceutical therapy. Other candidates may include patients who have been treated with EBRT to the maximum normal tissue tolerance, or who have failed other systemic therapies and now have progressive/recurrent symptoms.

Relative contraindications to using bone-targeting radioisotopes include severe renal dysfunction and severe bone marrow suppression. However, no well defined guidelines exist that define lower thresholds of hematological counts. Routinely, the following values can be considered as relative contraindications for treatment: hemoglobin <9 mg/dL, leukocyte count <3500 and platelet count <100,000 [41,42,46]. However, in selected cases, patients with leukocytes >2400 and platelets >60,000 may be considered for treatment. Myelotoxicity with radiopharmaceuticals can range from mild to moderate, is usually reversible, and in most cases does not require intervention. Patients with renal dysfunction fail to clear radiopharmaceutical agents from the circulation, increasing risk of myelotoxicity. Therefore, patients with glomerular filtration rates (GFR) <30 ml/min should probably not be treated with radiopharmaceuticals, and in those with GFR <50 ml/min a 50% dose-reduction should be considered [28].

Patients with predominantly soft-tissue pain, unifocal lesions, osteolytic lesions, and those with imminent spinal cord compression or pathological fracture should generally not be treated with these agents [47]. However, patients with ‘chronic’ spinal cord compression have been treated with radiopharmaceuticals in combination with corticosteroids [48].

Patients with a life expectancy <4 weeks are unlikely to benefit from radiopharmaceutical therapy due to the latency of therapeutic effect [49].

4. Clinical efficacy

4.1. Strontium-89 chloride

Strontium-89 chloride (Sr-89) is a divalent ion that (like calcium) is incorporated into the inorganic matter of bone when injected intravenously. The fraction that localizes to the bone is proportional to the tumor burden and ranges from 20% to 80% of the administered dose, with a 10-fold proclivity for metastatic tumor compared to healthy bone [50,51]. Several studies have investigated the relationship between the dose of strontium-89 and clinical responses in terms of bone pain palliation. A phase I/II study reported mean time-to-onset of response at 9 days with average duration-of-response of 1.6 months in patients receiving doses ranging from 1.0 to 4.0 mCi/kg [52]. Laing et al. reported no dose-response relationship with increasing Sr-89 doses from 1.5 to 3.0 MBq/kg [53]. In contrast, a retrospective review of dose-escalation studies found a positive correlation between increasing doses of Sr-89 and pain response [54]. The mean duration of pain relief reported in this review was about 6 months. A probable explanation for this discrepancy between studies is the non-uniformity across institutions regarding the definition of clinical response and the small number of patients studied. The consensus on the recommended safe dose for Sr-89 is 4 mCi/kg (148–150 MBq/kg).

Multiple randomized trials have been conducted evaluating the efficacy of Sr-89. Pain reduction was the most widely used response criterion in these trials. Most studies used graded pain scoring systems, but the inter-study variability limits comparisons between studies. Other efficacy criteria included analgesic consumption, quality-of-life indices, and tumor markers (*e.g.* PSA). All phase I–III trials investigating the clinical efficacy of Sr-89 have been summarized in Table 2. In a crossover double-blind trial, Lewington et al. examined the role of Sr-89 vs. placebo in patients with bone-metastatic prostate cancer and found that Sr-89 was superior in terms of pain response at the time of the first assessment ($P < 0.01$) and at the time of all subsequent assessments ($P < 0.03$) [55]. Furthermore, complete pain relief was only seen in patients treated with Sr-89. The absolute risk reduction for patients achieving pain relief with Sr-89 was 0.32 (95% confidence interval: 0.04–0.68). In contrast, another double-blind study found no significant difference in pain relief between Sr-89 and placebo, but survival at 2 years was higher in the Sr-89 arm (46% vs. 4%, $P < 0.05$) [56].

Finlay et al. published a systematic review summarizing the efficacy of Sr-89 and reported that complete pain response varied from 8% to 77% with a mean value of 32% [46]. The mean percentage of patients with a partial pain response was 44%. The time delay until the onset of treatment effect varied from 4 to 28 days, with the mean duration of response lasting 15 months. Reduction in analgesic use was between 71% and 81%. Consistent with this publication, another review reported that up to 80% of selected patients with osteoblastic metastases showed some response to therapy with Sr-89 with at least 10% patients becoming pain-free [57]. The duration of clinical response varied from 3 to 6 months.

It has been suggested that patients with bone-metastatic prostate cancer should be treated earlier in their disease course, and that radiopharmaceuticals should be initiated even if patients do not have pain in all radiographically-detected lesions [58]. This may lead to longer pain-free intervals and a longer transition to other therapeutic approaches including opioids. Although conclusions about retreatment with Sr-89 are difficult to draw, studies have shown that patients can be effectively retreated if they responded well to the first treatment [59]. However, patients who fail to respond well to the first dose are unlikely to benefit from retreatment [53,60].

The toxicities associated with Sr-89 are mostly mild and usually reversible. Leukopenia is common, with a leukocyte reduction of 10–65% observed in 20–80% of patients. Thrombocytopenia is present in 30–80% of patients [46]. Leukocyte and platelet nadir counts usually occur at 4–8 weeks following injection [57]; recovery to baseline ensues in 3–4 months even without intervention. Serious hematological toxicity is rare, and may reflect a patient's advanced disease state. Regular hematological monitoring is advised in strontium-treated patients.

4.1.1. Combination with radiotherapy—The treatment of choice for unifocal bone metastases is EBRT. However, in patients with multifocal disease, wide-field radiation is associated with short-term and long-term toxicity. The TransCanada Strontium-89 Study was a significant trial that aimed to evaluate the role of Sr-89 as an adjuvant to local-field external-beam irradiation in treatment men with CRPC [61]. The study found that adding Sr-89 to EBRT reduced analgesic requirements, and that the intervention group had approximately 50% less painful sites per patient compared to placebo ($P < 0.002$) with longer median time to further radiotherapy (35.3 vs. 20.3 weeks, $P = 0.006$). The study also demonstrated a significant difference in tumor marker (PSA and alkaline phosphatase) reductions after treatment ($P < 0.01$). Moreover, the Sr-89 group reported superior quality-of-life ($P = 0.006$), with better alleviation of pain and improved physical activity in the intervention group ($P < 0.05$). As suggested by earlier studies, hematological toxicities were more frequent in the Sr-89 group, with 3 documented cases of clinical bleeding from thrombocytopenia.

Another trial evaluated the role of Sr-89 as an adjuvant to radiotherapy in 95 patients with CRPC and found that there was no statistically significant difference in disease progression in the two groups [62], although the study was underpowered and closed early due to poor accrual. Baseline quality-of-life dimensions and changes in quality-of-life at 3 months were not different in the two arms. However, there were larger declines in alkaline phosphatase levels at 6 and 12 weeks in the Sr-89 arm compared to placebo ($P = 0.001$). Hematological events were more common in the Sr-89 group, although these were mainly grade ≤ 2 toxicities. A phase III study of the European Organization for Research and Treatment of Cancer–Genitourinary Group (EORTC–GU) compared Sr-89 vs. palliative local-field radiotherapy [63]. This study found no difference in subjective pain responses, analgesic consumption, or performance status. There was also no difference in progression-free survival. Surprisingly, the group receiving local-field radiotherapy demonstrated a trend towards longer overall survival than the Sr-89 group (11.0 vs. 7.2 months; $P = 0.046$).

Another pivotal trial (UK Metastron Investigators' Group Study) evaluated 284 patients with bone-metastatic CRPC and randomized them to receive Sr-89 or external-beam irradiation (further stratified to receive local or hemibody radiation) [64]. The authors found that all treatment groups demonstrated effective pain relief and there was no difference in overall survival. However, patients treated with Sr-89 had fewer new sites of pain than men undergoing local or hemibody radiotherapy ($P < 0.05$). Eventually, 12 patients in the local-radiotherapy group and only 2 in the Sr-89 group required additional radiation to a new osseous site ($P < 0.01$). In terms of myelotoxocity, grade-3/4 thrombocytopenia was documented with 11 patients (6.9%) in the Sr-89 group and 5 men (3.4%) in the radiotherapy group. Grade-3 leukopenia was seen in 5 patients (3.1%) receiving Sr-89.

4.1.2. Combination with chemotherapy—One potential way to enhance the clinical efficacy of Sr-89 would be to combine this modality with chemotherapy for metastatic CRPC. Several phase I/II studies have been conducted to evaluate the optimal safe dosing of chemotherapeutic agents in conjunction with Sr-89 and to determine the efficacy of such combinations [65,66]. In an initial dose-escalation study, Pagliaro et al. reported that an overall response rate >10% was unlikely using gemcitabine in concert with Sr-89 (although gemcitabine is not particularly active in prostate cancer). In a phase II study, it was shown that the combination of alternating weekly chemohormonal therapies with Sr-89 resulted in favorable progression-free and overall survival with acceptable toxicity [65]. A >50% reduction in PSA was maintained for 16 weeks in 77.7% of patients and for 32 weeks in 66.7% of men.

Further efforts to delineate the role of chemotherapy in enhancing the efficacy of Sr-89 have relied on randomized clinical trials. Sciuto et al. randomized 70 patients into two arms, one receiving standard 150 MBq Sr-89 with 50 mg/m^2 cisplatin (arm A) and the other received Sr-89 plus placebo (arm B) [67]. They found that overall pain relief occurred in 91% of patients in arm A and 63% of patients in arm B ($P < 0.01$) with a median duration of 120 days in arm A and 60 days in arm B ($P = 0.002$). Progression of bone disease was found in 27% of patients in arm A and 64% patients in arm B ($P = 0.01$). No differences in survival or hematological toxicity were noted in the two groups. In another study, Nilsson et al. compared the palliative efficacy of Sr-89 against a multi-drug chemotherapy regimen (5-fluorouracil, epirubicin, mitomycin-C) for palliation of bone pain in patients with bone-metastatic prostate cancer [68]. This study concluded that both groups had a significant reduction in pain intensity and frequency after 3 weeks compared to baseline ($P < 0.01$). The effect of chemotherapy on pain was thought to be due to an inhibitory effect on inflammation.

In another study, Tu et al. randomized 72 patients to receive doxorubicin with or without Sr-89 following induction therapy using ketoconazole and doxorubicin alternating with estramustine and vinblastine [69]. For the 36 patients assigned to Sr-89 plus doxorubicin, median survival was 27.7 months (range 4.9–37.7), and for the 36 who received doxorubicin alone, survival was 16.8 months (range 4.4–34.2) ($P = 0.001$; hazard ratio 2.76; 95%CI 1.44–5.29). The significance of this study was that it reported improved survival with therapy involving a radiopharmaceutical agent, something which had not been observed in other trials. Collectively, these studies suggest that radiopharmaceutical fortification with

chemotherapy is effective with definite improvements in clinical pain responses. However, uniformity of pain assessment and quality-of-life measurement is strongly warranted to devise effective guidelines for management of bone pain in such patients.

4.2. Samarium-153 lexidronam

First approved for use in the 1990s, samarium-153 quickly became one of the most widely tested radiopharmaceutical agents. Its complex with EDTMP rapidly localizes to bone in association with hydroxyapatite with an affinity which is five times higher for metastases than for normal bone [70]. This allows a preferential exposure of metastatic lesions with lower toxic effects on non-malignant tissue. The serum half-time clearance of this agent is rapid with 4–34% remaining in the blood 1 h after injection [41,71]. Kidneys are the main route of elimination with complete excretion of the agent within 6 h [38]. No change in urinary excretion of Sm-153 occurs with change in dose [72].

Table 3 summarizes clinical trials involving Sm-153 with respect to efficacy results and toxicity profiles. Many dose-escalation studies have described the toxicity and efficacy of increasing doses of Sm-153 [38,73–76]. As with Sr-89, myelosuppression is the usual side-effect with dose-limiting thrombocytopenia seen in 20–42% of the patients [46]. In a Phase I trial, 29 patients were treated with increasing doses of Sm-153 (0.25–2.0 mCi/kg, in 0.25 mCi/kg increments). Only two patients (7%) developed grade-3 hematological toxicity. In another study, 83% of the patients with prostate or breast cancer experienced pain relief within 2 weeks of administration of Sm-153 [38]. The duration of pain relief from a single injection ranged from 4 to 35 weeks. The dose-limiting toxicity manifested mainly as thrombocytopenia (platelet counts $<100 \times 10^9$/L occurred in 42% of patients). However, myelosuppression was transient and platelet counts recovered within 10 weeks of treatment.

Phase III placebo-controlled trials evaluating the efficacy of Sm-153 in prostate cancer patients have been completed. Serafini et al. randomized 118 patients with prostate ($n = 78$), breast ($n = 21$), lung ($n = 6$) and other ($n = 13$) cancers to receive either 0.5 or 1.0 mCi/kg Sm-153 vs. placebo in one double-blind placebo-controlled trial [77]. Patients receiving 1.0 mCi/kg of Sm-153 had 52–72% reduction in pain during each of the first 4 weeks ($P < 0.016$) with complete pain relief in 31% of patients by week 4. Durable pain relief was seen in 43% of patients for up to 4 months. A significant correlation was found between reduction in analgesic use and pain score ($P = 0.01$). Patients receiving Sm-153 had reductions in leukocyte and platelet counts to a nadir at 4–5 weeks. The leukocyte nadir in the low-dose Sm-153 group was 59% of baseline and in the higher-dose group was 51% of baseline. Leukocyte counts returned to baseline at 8 weeks without intervention. No grade-4 hematological toxicities were observed.

In another randomized double-blind phase III trial, 152 men with bone-metastatic CRPC were randomized to receive either the radioactive or nonradioactive samarium–lexidronam complexes in a 2:1 ratio [78]. Pain was measured using validated patient-derived visual analog scales (VAS) and pain descriptor scales (PDS). There was a significant improvement in pain in the treatment group vs. placebo, reflected by both VAS and PDS. In the treatment arm, VAS scores correlated significantly with decreased opioid use ($P = 0.0004$). Complete pain relief was reported in 38% of patients in the active group vs. 18% in the control group

($P = 0.008$). Transient myelosuppression was the only side-effect of Sm-153. Grade-3 thrombocytopenia and leukopenia were seen in 3% and 5% of patients, respectively. There were no grade-3 toxicities in the placebo arm. Pain flare occurred with equal frequency in both groups without any difference in overall response between the two groups.

In a separate study, 55 patients received single doses of Sm-153 at 0.5 mCi/kg and 59 patients received doses of 1.0 mCi/kg [72]. About 55% of the low-dose and 70% of the high-dose patients experienced some pain relief at week 4. Patients receiving 1.0 mCi/kg had a statistically significant reduction in area-under-the-pain-curve at weeks 3 and 4 compared to baseline ($P < 0.005$) whereas no such changes were seen in the low-dose group. Furthermore, a significantly higher number of patients were able to sleep through the night in the higher-dose group compared to baseline (33–59%, $P = 0.026$); this relationship was not seen in the lower-dose group. Leukocyte and platelets counts reached nadirs at 3–4 weeks and recovered by 8 weeks. Nadirs were lower in the 1.0 mCi/kg group than in the 0.5 mCi/kg group. Three patients in the lower-dose group and 1 in the higher-dose group developed grade-3 leukopenia but only after they received external-beam radiation therapy. Additionally, 3 and 2 patients in the lower-and higher-dose groups, respectively, developed grade-4 thrombocytopenia (3 of these also received external-beam radiation). In summary, Sm-153 leaves much to be desired with regard to overall survival benefits as trials failed to demonstrate any convincing evidence of such an effect, but it still remains a reasonable option for palliative effects.

4.2.1. Combination with chemotherapy—To study the role of samarium-153 in combination with chemotherapy in men with metastatic CRPC, 28 patients were treated in six cohorts using escalating doses of docetaxel from 65 to 75 mg/m^2 followed by Sm-153 at doses of 0.5–1 mCi/kg in a phase I study [79]. Each cycle lasted 6 or 9 weeks. Maximum tolerated doses were not reached, because full doses of both agents were well tolerated, even using an every-6-week dosing schedule of Sm-153. Fifteen patients had a >50% decline in PSA. One partial radiographic response was seen among the six patients with measurable disease. Bone markers including osteocalcin and serum and urine N-telopeptides changed significantly as a result of treatment. Neutropenia and thrombocytopenia were the commonly observed hematological toxicities. Leukocyte counts returned to normal without intervention. Three patients had prolonged thrombocytopenia which took longer than 4 cycles to recover.

A phase II trial enrolled 43 patients who had stable or responding disease after four cycles of induction chemotherapy with docetaxel and estramustine and gave them consolidation docetaxel 20 mg/m^2/week for 6 weeks plus Sm-153 during week 1 [80]. PSA-progression free survival (PSA–PFS) was the primary endpoint. PSA response was seen in 77% and pain response in 69% of patients. Median PSA–PFS was 6.4 months (95%CI: 6.0–7.0 months) and clinical PFS was 15 months (95%CI: 11–29 months). Median survival was 29 months (95%CI: 22–31 months). There was no febrile neutropenia, and only 2 episodes of reversible grade-3 thrombocytopenia were observed. Thus, combination of Sm-153 with chemotherapy remains a viable option for select patients who might retain sensitivity to chemotherapy after initial response to treatment, and future trials are warranted to explore this area further.

4.3. Rhenium-186 etidronate

^{186}Re-1,1-hydroxyethylidene-diphosphonate (HEDP) was recognized in the late 1980s as a potential radiotherapeutic agent for treatment of bone metastases. Table 4 summarizes the clinical trials that have investigated Re-186. Some of the initial phase I/II studies examined the safety and efficacy of Re-186 [81–83]. In one such study, 11 of the 14 patients with disseminated prostate cancer treated with Re-186 were completely pain free at the conclusion of the study [81]. The pain improvement was noted within 2 weeks in 8 of the responding patients and mean duration of pain relief after the first course of Re-186 was 6 weeks. Consistent with other studies, hematological toxicities were generally mild and transient. Grade-2 thrombocytopenia was observed in three patients with 1–2 week duration, and grade-2 leukopenia occurred in three patients. Five of the responding patients also reported an improvement in daily activities and two patients reduced/discontinued narcotic analgesics. Another phase II trial reported similar findings with a pain response in 67% of prostate cancer patients and a mean duration of response of 45 days [82]. These phase I/II trials paved the way for phase III randomized control trials using this agent.

To examine the clinical efficacy of Re-186, Scuito et al. treated 60 patients with painful bone metastases from different tumors (predominantly prostate cancer patients) with 1406 mBq of Re-186 [84]. Pain response was graded as complete, partial, minimal or absent using the Wisconsin test scoring system. Overall, 80% patients experienced pain relief, with 31% of patients reporting complete, 34% partial, and 15% minimal responses. The duration of pain relief ranged from 3 to 52 weeks, had a positive correlation with the degree of pain response ($P = 0.02$), and had a negative correlation with pretreatment scintigraphic scores and alkaline phosphatase levels ($P = 0.02$). Hematological toxicity was mild (only grade 1–2) and transient. Mean platelet counts decreased by 32% at 3 weeks and 18% at 4 weeks.

The PLACORHEN study was a pivotal phase III randomized double-blind trial wherein 111 men with bone-metastatic CRPC were randomized to receive either Re-186 or placebo [85]. A positive response day was defined as a day on which pain intensity was reduced by >25% compared with baseline or on days when pain intensity was reduced by <25% and medication index or daily activities improved by >25%. The total response (%) was defined as the number of positive response days divided by the number of days of follow-up. This varied from 0% to 96% (mean 27%) in rhenium-treated patients and from 0% to 80% (mean 13%) in the placebo-treated patients ($P < 0.05$). The number of patients who requested to have subsequent radiotherapy was higher in the placebo group vs. the Re-186 group (hazard ratio 1.51, $P = 0.069$). Pain response with Re-186 was found to be longer than that associated with placebo.

In another double-blind cross-over trial, 20 patients were treated with either Re-186 or placebo and followed up for 12 weeks [86]. The primary endpoint was the pain index, and the analgesic index was the secondary end point. At 3 weeks post-injection, the group receiving Re-186 had a 22% reduction in pain index whereas the placebo group had a 39% increase in pain ($P < 0.05$). Since this was a crossover study, patients in the control group could cross over to receive Re-186 after 4 weeks. In these patients, a significant pain response was documented with the subsequent administration of Re-186 ($P < 0.05$).

However, these changes in pain scores were not concurrently associated with a decline in analgesic index. Also, when comparing toxicities between the two groups, only leukopenia was increased with Re-186 vs. placebo, and no differences were observed in platelet counts between the two groups.

4.4. Comparative efficacy of radiopharmaceuticals

Some investigators have examined head-to-head comparisons between various bone-seeking radioisotopes in patients with osteoblastic metastases to determine their relative efficacy. Liepe et al. compared the efficacy of Re-186, Sm-153 and Sr-89 in 79 patients with painful bone metastases [87,88]. Efficacy was studied by its impact on pain symptoms, quality-of-life (using Karnofsky performance status) and bone marrow function. This study found that 73% of patients had some relief in their pain. However, there was no difference between the different radionuclides used with respect to pain palliation, performance status, or bone marrow toxicity ($P > 0.05$). In another study, the authors compared Sr-89 with Sm-153 in 100 patients with bone-metastatic prostate and breast cancers [89]. Again, there were no significant differences between the two agents for bone palliation. Analgesic effects were found to be persistent even after 4 months in about 80% of patients, especially in those with osteoblastic metastases. Hematological toxicities were transient and baseline counts returned in 1–4 weeks. Additional direct comparative studies between these agents are warranted in the future to better define the comparative efficacy of these bone-seeking radiopharmaceutical drugs.

4.5. Radium-223 chloride

Despite achieving significant palliative benefits in patients with painful bone metastases, all the bone-seeking radiopharmaceuticals discussed above have failed to produce improvements in survival. Accordingly, they have been FDA-approved and are indicated for pain palliation only. These agents are β-emitters with track lengths up to a few millimeters resulting in collateral bone marrow toxicity. In contrast, α-particles provide more dense ionizing radiation, called high-linear-energy-transfer radiation, in a narrow range of <100 μm (corresponding to 2–10 tumor cell diameters), minimizing myelotoxicity due to the short track-length [90]. These α-particles induce DNA double-strand breaks, rendering the DNA repair machinery essentially paralyzed against such radiation [91]. This also means that micro-metastases residing in the dormant G_0 cell cycle growth phase are not resistant to the effects of α-particles.

After multiple preclinical studies had supported the hypothesis that bone-targeted α-emitters had therapeutic effects on bone metastases [92,93], multiple agents were considered for possible *in vivo* testing. Radium-223, which acts as a calcium mimic, was chosen for extensive preclinical evaluation because it has natural bone-seeking proclivity without requiring a carrier, has a suitable half-life ($t_{1/2}$ = 11.4 days) allowing convenient dosing, and has a safe short-lived radon daughter isotope (^{219}Rn with $t_{1/2}$ = 4.0 s) [90]. The total skeletal uptake of Ra-223 in patients with osteoblastic metastases is estimated to range between 40% and 60% of the administered dose [43]. One study compared the biodistributions of Ra-223 and Sr-89 in mice by conducting dosimetric calculations for soft tissues and bone at various time points [93]. Encouragingly, both agents were strongly concentrated in the bones

compared to soft tissues. Ra-223 uptake in bone increased up to 24 h without significant redistribution of daughter nuclides from bone (2% at 6 h and <1% at 3 days). These experiments demonstrated that Ra-223 had an important advantage of reduced bone marrow toxicity.

Further studies were also undertaken to study the therapeutic efficacy of Ra-223 in nude rat models [94]. In one such study, animals were injected with MT-1 human breast cancer cells and were treated with either placebo or Ra-223. While all the untreated animals had to be sacrificed due to tumor-induced paralysis, animals treated with ≥ 10 kBq of Ra-223 showed a significantly increased survival. After 67 days, 40% of rats treated with Ra-223 were still alive compared to 0% in the control group ($P < 0.05$). Treatment with bisphosphonates was also unable to confer a survival advantage in this animal model. These encouraging preclinical studies led to the design of several clinical trials to test the safety and efficacy of Ra-223 in patients with bone-metastatic prostate cancer. These clinical trials are summarized in Table 5, and discussed below.

A phase I study was initially undertaken wherein Ra-223 was administered to 25 breast and prostate cancer patients with osseous metastases [90]. Each patient received one injection of Ra-223 as a part of a dose-escalation study design. Five patients comprised each dose-level, starting at 46 kBq/kg and then increasing to 93, 163, 213, and 250 kBq/kg. Patients were monitored for adverse effects and followed for 8 weeks. Dose-limiting toxicities were defined as platelets $<20 \times 10^9$/L, or neutrophils $<0.5 \times 10^9$/L. Palliative response was judged using a pain scale of the European Organization for Research and Treatment of Cancer (QLQ C30 questionnaire) [95]. Pharmacokinetic studies showed that Ra-223 did not remain in the blood for long, with <1% blood levels remaining at 24 h, and was predominantly eliminated via the intestinal route. Pain relief was reported by 52%, 60%, and 56% of patients after 1 week, 4 weeks, and 8 weeks respectively. However, no clear dose-response relationship could be established. A ‘flare’ phenomenon was observed in 28% of patients in the first week post-treatment. A decline in serum alkaline phosphatase levels was observed commonly in the prostate cancer cohort compared to the breast cancer cohort (52.1% vs. 29.5%, $P = 0.003$). This suggested that Ra-223 preferentially targeted osteoblastic rather than osteolytic bone metastases.

Dose-limiting hematological toxicity was not seen at any dose-level. Myelosuppression was predominantly seen at the highest dose-levels, was mild and reversible with a nadir 2–4 weeks after drug administration, and a return to baseline during the followup period. Only grade-1 thrombocytopenia was observed even at the highest dosages. Grade-3 neutropenia and leukopenia occurred in two and three patients respectively. The toxicity profile of Ra-223 was somewhat different from that of β-emitters which mainly induce thrombocytopenia. Twenty two of the 25 patients experienced adverse effects, 98% of which were mild-to-moderate in intensity. These consisted of transient diarrhea (10 of 25 patients), fatigue (5 of 25), and nausea/vomiting (5 of 25). While diarrhea occurred at all dose-levels (probably a result of predominant intestinal elimination), nausea/vomiting occurred only at the highest doses.

After encouraging phase I results, Ra-223 was the subject of a phase II double-blind placebo-controlled trial which randomized 64 patients with CRPC to receive 4 intravenous injections of either 50 kBq/kg Ra-223 (33 patients) or placebo (31 patients), given every 4 weeks beginning on the day of EBRT [96]. Primary endpoints were change in bone-alkaline phosphatase, and time to skeletal-related events (SREs). The study had 80% power to detect an absolute difference of 15% between treatment and control groups with respect to mean change in alkaline phosphatase. PSA response and disease progression were also included as endpoints, and were defined according to the Prostate Cancer Working Group guidelines [97]. Median change in bone-alkaline phosphatase from baseline to 4 weeks was −65.6% (95%CI: −69.5 to −57.7%) in the Ra-223 group and +9.3% (95%CI: 3.8–60.9%) in the placebo group ($P < 0.0001$). Compared to placebo, Ra-223 also induced significant reductions in all other bone biomarkers tested: total-alkaline phosphatase, procollagen-I-N-propeptide, serum C-telopeptide of type-I collagen, and type-I collagen crosslinked C-telopeptide. Time-to-first-SRE was not significantly different in the two groups (14 vs. 11 weeks, $P = 0.26$; hazard ratio 1.75, 95%CI: 0.96–3.19). Median time-to-PSA-progression was 26 vs. 8 weeks for Ra-223 and placebo respectively ($P = 0.048$). Median relative change in PSA from baseline to 4 weeks was −23.8% (range: −98.6 to +545.6%) in the Ra-223 group and 44.9% (range: −91.3 to +563.5%) in the placebo group ($P = 0.003$). The two arms did not significantly differ in overall survival, although a favorable trend was seen in favor of Ra-223 (65.3 vs. 46.4 weeks, $P = 0.066$). After adjusting for baseline covariates, the hazard ratio for survival was 2.12 (95%CI: 1.13–3.98, $P = 0.02$), suggesting a potential survival advantage with Ra-223.

Hematological toxicities in this trial were similar in the two groups. Thrombocytopenia was not observed in the Ra-223 group or the placebo arm. Grade-2 neutropenia was seen in 3 patients receiving Ra-223 but none receiving placebo. Myelotoxicity was non-cumulative and observed only during the first 4 weeks of treatment. There were 12 serious adverse events in the Ra-223 arm and 19 in the placebo arm. However, most of these events were deemed unrelated to study treatments.

Following successful results in phase II trials with a possible suggestion of survival benefit, radium-223 was the subject of a pivotal randomized placebo-controlled phase III trial (ALSYMPCA: Alpharadin in Symptomatic Prostate Cancer), the results of which were recently presented at the American Society of Clinical Oncology-Genitourinary Symposium (ASCO-GU) [98]. This study randomized 922 participants with symptomatic bone-metastatic CRPC (in a 2:1 ratio) to receive 6 injections at 4-weekly intervals of either Ra-223 (50 kBq/kg) or placebo. Patients were required to be symptomatic with ≥ 2 bone metastases, without visceral metastases, and had either received docetaxel previously or were unfit for docetaxel chemotherapy. The study examined overall survival as its primary endpoint, with 3 years of follow-up planned. Secondary endpoints included time-to-first-SRE, time to alkaline-phosphatase progression, alkaline-phosphatase response, alkaline-phosphatase normalization, time-to-PSA-progression, safety, and quality-of-life. The study was designed with 90% power to detect a hazard ratio for death of 0.76 at the 5% significance level; it would require 310 events for a planned interim analysis. At the time of

this interim analysis, the authors reported data from 809 randomized patients (541 on Ra-223, 268 on placebo) and 314 events.

Analysis showed that the two groups were similar at baseline with regard to patient demographics (age, race), disease characteristics (performance status, extent of disease, pain index), and laboratory parameters (hemoglobin, albumin, total alkaline-phosphatase, lactate dehydrogenase, PSA). At the planned interim analysis, 50% of Ra-223 patients and 35% of placebo patients had received all 6 injections of the study drug, while 21% and 19% of patients respectively were still undergoing treatment. Median overall survival was significantly superior in the Ra-223 arm (14.0 months) compared to the placebo arm (11.2 months), with a hazard ratio of 0.695 (95%CI: 0.552–0.875, $P = 0.0019$). The significantly improved overall survival in the treatment group met the predetermined boundary for stopping the trial early, and the Independent Data Monitoring Committee (IDMC) recommended termination of the trial on June 3, 2011 due to evidence of significant treatment benefit.

In subset analyses, the survival advantage of Ra-223 was maintained regardless of whether patients were using concurrent bisphosphonates (hazard ratio 0.582; 95%CI: 0.397–0.854) or not (hazard ratio 0.752; 95%CI: 0.567–0.999). Further analysis suggested that patients who had not previously received docetaxel had an improved survival (hazard ratio 0.611; 95%CI: 0.423– 0.883) while docetaxel-pretreated patients showed a non-significant trend towards improved survival (hazard ratio 0.755; 95%CI: 0.565–1.009). Finally, only patients with a baseline ECOG performance score of 0–1 appeared to achieve superior survival (hazard ratio 0.691; 95%CI: 0.535–0.892), while those with a score ≥ 2 seemed not to benefit (hazard ratio 0.731; 95%CI: 0.398–1.343).

Among the secondary endpoints, median time-to-first-SRE was significantly improved in the treatment arm compared to placebo (13.6 vs. 8.4 months; hazard ratio 0.610, 95%CI: 0.461–0.807, $P = 0.0005$). Similar improvements were observed in the Ra-223 arm with respect to time-to-alkaline-phosphatase-progression (hazard ratio 0.163; 95%CI: 0.121–0.221, $P < 0.00001$) and time-to-PSA-progression (hazard ratio 0.671; 95%CI: 0.546–0.826, $P = 0.0002$). These results suggest a significant improvement in controlling metastatic bone disease with Ra-223 compared to placebo. Furthermore, patients who had a total alkaline-phosphatase response (>30% reduction in alkaline-phosphatase levels) were significantly more common in the Ra-223 arm (43% vs. 3%, $P < 0.001$). In patients with baseline alkaline-phosphatase above the normal range, alkaline-phosphatase normalization was also significantly more frequent in the Ra-223 arm (33% vs. 1%, $P < 0.001$).

Adverse events (AEs) were determined for a total population of 762 men (those who received >1 study-drug injection). AEs were observed in 88% of Ra-223 patients and 94% of placebo-treated patients. Surprisingly, the percentage of patients experiencing serious AEs was also less in the Ra-223 cohort (43% vs. 55%). AEs resulting in treatment discontinuation occurred in 13% of men in the Ra-223 group and 20% in the placebo group. Grade-3/4 anemia was documented in 11% of men receiving Ra-223 and 12% receiving placebo; grade-3/4 neutropenia was present in 2% of Ra-223 patients and 1% of placebo-treated patients; and grade-3/4 thrombocytopenia occurred in 4% of men on Ra-223 and 2%

of men on placebo. These findings were somewhat surprising, because phase I and II trials had suggested a predominance of neutropenia from Ra-223 with minimal effects on platelets. Other notable grade-3/4 toxicities from radium-223 included bone pain (18%), nausea (2%), vomiting (2%), diarrhea (1%) and constipation (1%). These did not differ significantly with the placebo-treated patients.

The safety profile of Ra-223 is encouraging when compared to β-emitters, and might allow further studies with more liberal dosing and extended treatment periods. It has been shown that the high-intensity linear-energy-transfer α-radiation from Ra-223 has effective antitumor activity with selective sparing of the bone marrow [43]. This feature is of particular interest because myelosuppressive chemotherapy with docetaxel usually constitutes first-line systemic treatment for patients with symptomatic metastatic CRPC. Therefore, the use of Ra-223 (which has a favorable bone marrow toxicity profile) could potentially represent a paradigm-changing modality in patients who have previously received or might eventually receive docetaxel. Additionally, combination of Ra-223 with docetaxel would also be a conceivable strategy, and may offer synergistic clinical benefits. The low myelotoxicity could also allow earlier repeat dosing of Ra-223 without waiting for a full bone marrow recovery before proceeding with further treatment.

5. Summary

Both Sr-89 and Sm-153 have been shown through multiple clinical trials to be effective agents for bone pain palliation in men with symptomatic metastatic CRPC, without impacting the survival of these patients. They are currently the only FDA-approved bone-targeting radioisotopes for the treatment of metastatic CRPC. Ra-223 is the first radiopharmaceutical drug to demonstrate a prolongation of overall survival in these patients, but this agent also produces palliative benefits and reduces skeletal-related events as well. The survival improvement witnessed with Ra-223 comes on the heels of other recent data showing improvements in survival with sipuleucel-T, docetaxel, cabazitaxel, abiraterone, and MDV3100 (an oral androgen signaling inhibitor). Radium-223 therefore marks the sixth drug to improve survival for men with metastatic CRPC, representing an unprecedented moment in the treatment landscape for advanced prostate cancer.

However, the promise of Ra-223 may come with a number of unanswered questions. First, it is uncertain if the FDA-approval of this agent will limit its use to men with symptomatic disease, or whether the drug will be indicated both for chemotherapy-naïve and docetaxel-pretreated patients. In the authors' opinion, Ra-223 will most likely be approved for men with symptomatic bone-metastatic CRPC who have received prior docetaxel or are ineligible for docetaxel treatment, consistent with the eligibility criteria for the ALSYMPCA study. However, because of the survival benefit observed, some might argue that Ra-223 should be indicated for all men with CRPC and bone metastases, independent of the presence or absence of symptoms. Second, the potential long-term toxicities of Ra-223 have not been fully established, primarily because median survival for men on the ALSYMPCA study was short. It is conceivable, for example, that there might be a risk of secondary malignancies as a result of prior treatment with Ra-223 that has not yet emerged. This risk could be higher if

the agent is used in patients who are asymptomatic with minimal metastatic burden, where the expected survival may be 2–3 years or longer.

Third, it has not yet been established if Ra-223 can be safely administered concurrently with docetaxel, or if dose-reductions of both agents may be required for safe administration. To this end, a phase I combination study (NCT01106352) is currently enrolling patients to investigate the optimal combination of docetaxel with Ra-223 in men with bone-metastatic CRPC. Finally, an additional attractive use of Ra-223 would be in men with non-metastatic CRPC, in an effort to prolong metastasis-free survival in these patients. However, since Ra-223 might require osteoblastic bone turnover to bind to osseous metastases, its use in the non-metastatic (or micro-metastatic) setting may be less rational. While these questions will certainly need to be answered in the next 5 years, the addition of a novel radiopharmaceutical agent to our treatment armamentarium will undoubtedly be a welcome option for oncologists and prostate cancer patients alike seeking life-prolonging therapies for the management of this disease.

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Table 1

Comparison of physical characteristics of common radiopharmaceuticals.

Radiopharmaceutical	Half-life ($t_{1/2}$)	Maximum beta (β) energy in MeV (mean)	Mean alpha (α) energy in MeV	Mean gamma (γ) energy in keV	Maximum tissue penetration (mean)	Standard dose (SI units)
Strontium-89	50.5 days	1.46 (0.58)	–	0	5.5 mm (2.4 mm)	4 mCi/kg (148 MBq/kg)
Samarium-153	1.9 days	0.81 (0.22)	–	103	2.5 mm (0.6 mm)	1 mCi/kg (37 MBq/kg)
Rhenium-186	3.8 days	1.07 (0.35)	–	137	4.5 mm (1.1 mm)	35 mCi (1295 MBq)
Radium-223	11.4 days	–	5.64	–	<0.1 mm	1.35–6.75 kCi/kg (50–250 kBq/kg)

Table 2

Summary of trials of strontium-89 for metastatic prostate cancer.

Study	Treatment description (# patients)	Primary endpoint	Results	Other outcomes	Adverse events	Comments
Pagliaro et al. [66] Phase I/II	Sr-89 with gemcitabine (4 patients received 600 mg/m^2, 11 received 800 mg/m^2)	PSA response	No patient achieved partial response (>80% reduction in PSA)	Overall survival (OS) 8 mos	Dose level 2 (neutropenia in 26.7%, thrombocytopenia 53.3%, anemia in 26.7%)	–
Laing et al. [53] Phase I/II	Sr-89 (83)	Pain response using non-standardized scale at 12 weeks	75% with some pain relief and 22% pain-free	–	No grade-3/4 hematological adverse effects	Pain relief began in 6 weeks and lasting for 4–15 months
Buchali et al. [56] Phase I/II	Sr-89 (25) vs. placebo (24)	Pain response	36.8% pain response in Sr-89 vs. 50% placebo	2 year survival was 46% in Sr-89 vs. 4% placebo ($p < 0.05$)	Leukopenia, 12% in Sr-89 vs. 4.2% in placebo; thrombocytopenia, 50% in Sr-89 vs. 23.5% in placebo	–
Nilsson et al. [68] Phase II	Sr-89 (18) vs. 5-FU, epirubicin, mitomycin-C (17)	Pain response using a verbal scale	At 3 wks, pain reduced in both groups ($p = 0.01$ and 0.001 respectively)	No difference in Karnofsky performance status or analgesic use	More severe side-effects in chemotherapy group ($p < 0.05$)	–
Porteret al. [61] Phase III	Local XRT plus Sr-89 (68) vs. Local XRT plus placebo (58)	Pain response using RTOG criteria. Analgesic use. QoL using Visual analog scale	At 3 mos, complete pain relief 50% (Sr-89) vs. 36% (placebo); discontinuation of analgesics 17.1% (Sr-89) vs. 2.4% (placebo), $p < 0.05$	Greater improvement in pain and physical activity with Sr-89 ($p < 0.05$); OS: 6.3 mos (Sr-89) vs. 7.9 mos (placebo), $p = 0.6$	Leukopenia grade-3/4: 12% in Sr-89 vs. 0% in placebo; thrombocytopenia grade-3/4: 32.8% in Sr-89 vs. 3.4% in placebo	Time to further XRT 35.3 mos (Sr-89) vs. 20.3 mos (placebo), $p = 0.006$; # new painful sites 0.59 (Sr-89) vs. 1.21 (placebo), $p < 0.002$
Turner et al. [48] Phase III	Sr-89 (93)	Pain response using RTOG criteria; QoL using FLIC index	At 3 mos, complete pain relief in 17.6% and some pain relief in 62.4%	At 3 mos, median increase of 12.8 points on FLIC index	Leukopenia grade ≥ 2: 12%; Thrombocytopenia grade ≥ 2: 22%	Patients with any pain response had improved QoL ($p = 0.013$)
Smeland et al. [62] Phase III	Sr-89 plus EBRT (46) vs. Placebo plus EBRT (49)	Progression of disease (using QLQ C-30 questionnaire, pain score, analgesic requirement, WHO performance status)	No difference in disease progression rates	No statistical difference in QoL index in the two groups; No difference in OS	Leukopenia grade-1/2: 36.4% in Sr-89 vs. 13.3% in placebo ($p = 0.02$); Thrombocytopenia grade-1/2: 15.9% in Sr-89 vs. 4.4% in placebo	–
Scuito et al. [67] Phase III	Sr-89 plus cisplatin (35) vs. Sr-89 plus placebo (35)	Pain response and duration of response	Pain response in 91% (Sr-89) vs. 63% (placebo), $p < 0.01$; duration of pain relief 120 d (Sr-89) vs. 60 d (placebo), p0.002	OS: 9 mos (Sr-89) vs. 6 mos (placebo), $p = 0.30$	Anemia grade-3/4: 8.5% in Sr-89 vs. 11.4%; leukopenia grade-1/2: 22.9% in Sr-89 vs. 5.7% in placebo; thrombocytopenia grade1/2: 2.8% in Sr-89 vs. 5.7% in placebo	Bone disease progression in 27% (Sr-89) vs. 64% (placebo), $p = 0.01$
Quilty et al. [64] Phase III crossover	Sr-89 (76) vs. local XRT (72) Sr-89 (77)	Pain response, mobility and analgesic use	At 3 mos, 65.1% patients with relief in pain with Sr-89 vs. 66.7% with local XRT; 70% in	OS: 33 wks (Sr-89) vs. 28 wks (XRT), $p = 0.1$	Leukopenia grade-3: 3.1% in Sr-89 vs. 0% XRT; thrombocytopenia	Fewer new painful sites after Sr-89 ($p < 0.05$)

Study	Treatment description (# patients)	Primary endpoint	Results	Other outcomes	Adverse events	Comments
	vs. hemibody XRT (80) vs. hemibody XRT (80)		Sr-89 vs. 67.4% with hemibody XRT		grade-3/4: 6.9% in Sr-89 vs. 3.4% in XRT	
Oosterhof et al. [63] Phase III	Sr-89 (101) vs. Local field XRT (102)	Subjective response using pain score, analgesic use or performance status	Subjective response in 34.7% of Sr-89 group vs. 33.3% of XRT	OS: 11 mos (XRT) vs. 7.2 mos (Sr-89), $p = 0.0457$	No grade-3/4 leukopenia; 1 patient in Sr-89 with grade III toxicity	>50% decline in PSA in 13% with Sr-89 vs. 10% wiith XRT
Lewington et al. [55] Phase III crossover	Sr-89 vs. placebo (26)	Pain response	Complete pain response only in Sr-89; clinical response with Sr-89 better than placebo at first assessment ($p < 0.01$) and second assessment ($p < 0.03$)	–	Thrombocytopenia: grade- 3 toxicity in 12%, and grade-4 in 15.4%	–

Abbreviations: d: days; FLIC: Functional Living Index Cancer Instrument; mos: months; OS: Overall survival; QoL: Quality of life; RTOG: Radiation Therapy Oncology Group; XRT: External radiation therapy.

Table 3

Summary of studies describing therapeutic efficacy of samarium-153 in metastatic prostate cancer.

Study	Treatment (# patients)	Primary endpoint	Results	Other outcomes	Adverse effects	Comments
Collins et al. [75] Phase I/II	Escalated doses of Sm-153 from 1.0 mCi/kg to 2.5 mCi/kg (52)	Pain response	Overall pain response 76%	Median OS better with higher dose (9 mos vs. 6 mos, p = 0.03)	Increased hematological toxicity with higher dose	Higher dose experienced greater reduction in opioid use
Valicenti et al. [73] Phase I	Escalated doses of Sm-153 from 0.2 mCi/kg to 2.0 mCi/kg (29)	Grade ≥ 3 toxicity	–	–	Grade-3 anemia and/or thrombocytopenia in 3.57% of patients	Significant dose-response in nadir platelet count at 4 wks
Sandeman et al. [74] Phase I	Escalated dose of Sm-153 from 1.5 Gy to 4.5 Gy (9)	Pain relief	88.8% patients had at least some relief of pain	–	Thrombocytopenia in 44.4% patients	Pain relief delayed for 2 wks but maximal 4 wks
Dolezal et al. [76] Phase I	Sm-153 at dose of 40 MBq/kg (32)	Pain relief	At 3 mos, significant pain relief in 38% patients and some pain relief in 72%	–	2 patients had grade-3 hematological toxicity, no grade-4 toxicities	Reduction in analgesic requirement
Morris et al. [79] Phase I	Escalated doses of Sm-153 from 0.5 to 1.0 mCi/kg and docetaxel from 65 to 75 mg/m^2 (28)	Safety	15 patients had >50% decline in PSA	–	No dose-limiting toxicity	Significant changes in urine and serum N-telopeptides, and osteocalcin
Fizazi et al. [80] Phase II	Sm-153 with docetaxel (43)	PSA-PFS	Median PSA-PFS was 6.4 mos	Median OS was 29 mos	2 patients (5%) had grade-3 thrombocytopenia	PSA response in 77%, pain response rate 69%
Serafini et al. [77] Phase III	Sm-153 at 0.5 mCi/kg (40) or 1.0 mCi/kg (39) vs. placebo (39)	Pain relief	62–72% of patients had pain relief with 1.0 mCi/kg during first 4 wks and 31% had complete/ marked relief by wk 4	–	With 1.0 mCi/kg: grade-3/4 anemia in 6%, thrombocytopenia in 3% and leukopenia in 14% (compared to 35%, 0% and 0% respectively with placebo)	Significant correlation between reduction of analgesic use and pain scores (with 1.0 mCi/kg)
Sartor et al. [78] Phase III	Sm-153 (101) vs. placebo (51)	Pain relief	Significant improvement in bone pain and analgesic use with Sm-153 (p < 0.05)	–	With Sm-153: grade-3 thrombocytopenia in 3% and leukopenia in 5% (vs. none in placebo)	–
Resche et al. [72] Phase III	Sm-153 at 0.5 mCi/kg (55) vs. 1.0 mCi/kg (59)	Pain relief	Significant difference in pain scores between doses at wk 4 (p = 0.0476)	OS not different between groups	Mean leukocyte nadir and platelets lower with 1.0 mCi/kg than 0.5 mCi/kg	At wk 4, pain relief achieved in 55% for 0.5 mCi/kg and 70% with 1.0 mCi/kg

Abbreviations: mos: months; OS: overall survival; wks: weeks: PSA-PFS: Prostate-specific antigen-progression-free survival.

Table 4

Summary of clinical trials for evaluation of efficacy of rhenium-186 in patients with bone metastases.

Study	Treatment description (# patients)	Primary endpoint	Results	Other outcomes	Hematological adverse effects	Comments
Maxon et al. [83] Phase I/II	Re-186 (20)	Pain response	Complete pain relief in 25% and partial in 55%	–	Minimal	–
Tennvall et al. [81] Phase I/II	Re-186 (14)	Pain intensity response	Pain relief in 79% patients, 29% pain-free	Median survival was 6 mos in responders	Thrombocytopenia grade-2 and/or leukopenia grade-2 in 21.42% of patients	–
Kolesnikov-Gauthier et al. [82] Phase II	Re-186 (12)	Objective response using Pain index, analgesic index and performance index	Positive response (partial or complete) in 67% of prostate cancer patients	50% of patients had decrease in pain index, 58.8% in analgesic index, 16.6% had improvement in performance index	Thrombocytopenia grade-2 in 23% and leukopenia grade-2 in 17.5%	–
Sciuto et al. [84] Phase II	Re-186 (60)	Pain response using Modified Wisconsin scale	31% patients had complete and 80% overall some pain response	Pain relief correlated positively with degree of response ($p = 0.02$) and negatively with ALP ($p = 0.006$) and scintigraphic score ($p = 0.02$)	Thrombocytopenia (mean decline 32%) at 3 wks, leukopenia (mean decline 18%) at 4 wks	At 3 wks, significant improvement in Wisconsin score ($p < 0.001$), Karnofsky score ($p < 0.001$) and ALP levels ($p = 0.01$). Tumor markers decrease in 45% of patients at 4 wks
Han et al. [85] Phase III (PLACORHEN study)	Re-186 (59) vs. Placebo (52)	Number of positive pain response days	Mean percentage of pain response days 27% (Re-186) vs. 13% (placebo), $p < 0.05$	Median survival 37.2 wks (placebo) vs. 30.4 wks (Re-186), $p > 0.05$	–	Radiotherapy for pain required in 44% (Re-186) vs. 67% (placebo)
Maxon et al. [86] Phase III crossover	Re-186 (6) vs. Placebo (7)	Pain index	Significantly greater relief in pain with Re-186 ($p < 0.05$)	–	Significant leukopenia with Re-186 ($p < 0.01$)	–

Abbreviations: ALP: alkaline phosphatase; WBC: White blood cells; mos: months; wks: weeks.

Table 5

Summary of clinical trials on the therapeutic efficacy of radium-223 in men with prostate cancer.

Study	Treatment (# patients)	Primary endpoint	Results	Other outcomes	Hematological adverse effects	Comments
Nilsson et al. [90] Phase I	Escalated doses of Ra-223 (25)	Pain relief	At 2 mos, pain relief in 56% patients	Overall survival (OS) 20 mos	Thrombocytopenia grade-1 in 3 pts; leukopenia grade-3 in 3 pts: neutropenia grade-3 in 2 pts	Serum ALP nadir 29.5% in females and 52.1% males
Nilsson et al. [96] Phase II	Ra-223 (31) vs. placebo (33)	Change in ALP concentrations and time to skeletal-related events (SREs)	Change in ALP: 65.6% (Ra-223) vs. 9.3% (placebo), $p < 0.0001$; HR for time to first SRE 1.75 (0.96–3.19); Time to PSA progression 26 wks (Ra-223) vs. 8 wks (placebo), $p = 0.048$	OS: 65.3 wks (Ra-223) vs. 46.4 wks (placebo); $p = 0.068$	Thrombocytopenia grade-3: 0% in Ra-223 vs. 3.03% in placebo; neutropenia grade-2/3: 9.6% in Ra-223 vs. 0% in placebo	–
Parker et al. [98] Phase III (ALSYMPCA trial)	Ra-223 (541) vs. placebo (268)	Overall survival (OS)	OS: 14 mos (Ra-223) vs. 11.2 mos (placebo), HR 0.695, $p = 0.001$	HR time to total ALP progression: 0.163 ($p < 0.00001$), HR for time to PSA progression: 0.671 ($p = 0.0002$),	Anemia grade-3/4 in 11% in Ra-223 vs. 12% in placebo; neutropenia grade-3/4 in 2% in Ra-223 vs. 1% in placebo; thrombocytopenia grade-3/4 in 4% in Ra-223 vs. 2% in placebo	More patients with total ALP response and total ALP normalization in Ra-223 group

Abbreviations: ALP: alkaline phosphatase; HR: hazard ratio; PSA: prostate specific antigen; mos: months; wks: weeks.